Do risk factors for epithelial ovarian cancer have an impact on prognosis? Focus on previous pelvic surgery and reproductive variables

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Summary

Objectives: The prognostic impact of risk factors for ovarian cancer development is sparsely explored, but previous sterilisation has been shown to have a negative impact on survival.

Methods: Ovarian cancer cases were from the Danish MALOVA study. Information on previous pelvic surgery as well as reproductive variables was obtained from a personal interview conducted closely after primary surgery. Cox regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for ovarian cancer specific death in relation to previous pelvic surgery and reproductive variables including lifetime number of ovulation years.

Results: A total of 295 women with Stage III ovarian carcinomas were identified and followed to death or for a median of 7.3 years (range 5.4-9.5 years). Previously sterilised or hysterectomised women seemed to have a slightly decreased risk of ovarian cancer death (HR = 0.62; 95% CI: 0.36-1.08 and HR = 0.82; 95% CI: 0.55-1.21), although none of these associations reached statistical significance. The prognostic impacts of the individual reproductive variables followed the same pattern as the impact of the variables on ovarian cancer development, although significance was only reached for age at menarche (HR = 0.91 per year; 95% CI: 0.84-0.99). By accumulation of the possible minor effects of the reproductive variables in calculation of the total lifetime number of ovulation years, we found that survival decreased significantly with increasing number of ovulations (HR = 1.53 per 10 years; 95% CI: 1.09-2.14).

Conclusion: Increasing lifetime number of ovulations was a negative prognostic factor for ovarian cancer specific survival. Previous sterilisation or hysterectomy seemed to be associated with improved survival.

Key words: Sterilisation; Hysterectomy; Lifetime ovulation years; Risk factors; Prognosis; Ovarian cancer survival.

Introduction

Ovarian cancer is the sixth most frequent neoplasm regarding incidence as well as mortality in the developed countries [1]. Scandinavian countries are well known high-incidence areas [1]. The incidence has remained almost unchanged or has slightly declined in Scandinavia during the last two decades [2, 3], whereas the incidence has been increasing in the Eastern, and especially Southern European countries [3].

Epidemiological studies have identified factors associated with risk of ovarian cancer development: Nulliparity is associated with a 2-3 fold increased risk, while also early menarche and late menopause may increase risk of ovarian cancer [4]. Multiparity, use of oral contraceptives and previous sterilisation or hysterectomy are associated with a reduced ovarian cancer risk [4].

Factors affecting risk of ovarian cancer by yet unknown mechanisms presumably affect the growth of malignant ovarian cells and may continue to influence the growth of the malignant cells not eradicated by the primary treatment and thus the survival. Only one study has examined the prognostic impact of previous tubal ligation, finding that sterilised patients had significantly decreased survival compared to non-sterilised patients [5]. In the same study, no conclusions on the effect of previous hysterectomy could be made because of too few cases. It was suggested that sterilised women may develop a more aggressive form of ovarian cancer or a cancer more resistant to chemotherapy.

Only a few studies have examined the association between reproductive risk factors and survival following ovarian cancer. Women reporting more than two pregnancies had improved survival in one study [6], and two or more abortions were associated with improved survival in another study [7]. However, other studies found no prognostic impact of the number of pregnancies [8], or the number of childbirths [6-8]. No significant association between the age at menarche or menopause and ovarian cancer survival has been found [6-8]. Zhang *et al.* [9] examined the prognostic impact of e.g. oral contraceptive use, hormone replacement therapy and body mass index, and found that only pre-morbid body mass index had a prognostic impact, whereas no prognostic impact was found for previous hormone intake.

The aim of the present study, based on ovarian cancer cases from a population-based case-control study, was to evaluate the association between ovarian cancer survival and previous sterilisation, hysterectomy and selected reproductive factors among women with epithelial ovarian cancer Stage III.

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Materials and Methods

The MALOVA study

The present paper is based on the Danish MALOVA study (MALignant OVArian cancer study); a population-based multidisciplinary case-control study on ovarian cancer, covering epidemiology, biochemistry and molecular biology with the purpose to investigate risk factors and prognostic factors of ovarian cancer. The design of the MALOVA study is described in detail elsewhere [10, 11]. Briefly, an attempt was made to include all Danish women in the study area, aged 35-79 years, scheduled for an explorative laparotomy/laparoscopy because of the suspicion of ovarian tumour from December 1994 to May 1999. The study area consisted of gynaecologic hospital departments in the municipalities of Copenhagen and Frederiksberg and the counties of Copenhagen, Frederiksborg, Roskilde, Western Sealand, Storstroem, Funen, and Southern and Northern Jutland.

The participants had a preoperative blood sample taken and were personally interviewed postoperatively. The interview included for example socio-demographic variables, smoking habits, height and average weight in the last five years prior to the ovarian cancer diagnosis. Further, a lifetime calendar was used to gain detailed information about reproductive and gynaecologic history and lifetime use of hormones including oral contraceptives.

The study database was linked to the Danish Cancer Registry every second month to ensure that all eligible cases in the study area were included. If a woman was registered in the Danish Cancer Registry with ovarian cancer, but had not primarily been included in the study, she was contacted by letter and asked to participate in an interview.

Pathology reports and tissue specimens were collected from the participating hospitals and the histological type and grade were reviewed in a blinded fashion [11]. International Federation of Gynecology and Obstetrics (FIGO) stages were obtained from clinical records and were reviewed independently by two oncologic gynaecologists.

Study population

A total of 681 ovarian cancer patients were included in the MALOVA study, and in the present analyses we focused on the 295 women with epithelial ovarian cancer Stage III who participated in an interview, thereby excluding 28 with non-epithelial ovarian cancer, and 302 with Stage I, II or IV disease and 56 with Stage III, who only participated with a blood sample. The median time between surgery and interview was eight days (5-95 percentiles: 3-300 days). More than 74% were interviewed within nine weeks.

Follow-up

In Denmark every person has a unique personal 10-digit identification number encoding information of date of birth and sex. The Central Population Register, containing information on dates of birth, death and emigration, assigns the identification number to all residents shortly after birth and is updated on a daily basis. All cases were traced in this register and followed until death or 20, October 2004, whichever came first. In addition, all women were linked to a Danish hospital reference system and information about hospital admission to departments of oncology and gynaecology was obtained. The relevant hospital files were collected and information on treatment (surgery and chemotherapy), performance status at start of chemotherapy, and cause of death, if relevant, was retrieved. In cases where the cause of death was uncertain according to the patient's file, information was obtained from the Danish Causes of Death Register. At the end of the follow-up, 245 women had died of ovarian cancer, five had died of other causes and 45 women were still alive. The median follow-up time was 7.3 years (range 5.4-9.5).

Variables

To examine the prognostic effect of determinants for ovarian cancer development, we included information about past history of sterilisation and hysterectomy, as well as time since the surgery; use of and total use time of oral contraceptives; age at menarche and at menopause; number of pregnancies, as well as pregnancy outcome and length of pregnancy, age at first delivery, time since last delivery and the total breastfeeding time. The total number of ovulation years was calculated as the difference between age at last menstruation and age at menarche, minus the total years of oral contraception use, total years of pregnancy time (cumulative length of each pregnancy) and total years of breastfeeding. Women with missing information on any of these factors, as well as women with menses cessation influenced by hysterectomy or hormonal replacement therapy (HRT) were excluded from the calculation of ovulation years. As covariates we included age, histological type of tumour, radicality of primary surgery, first-line chemotherapy treatment, smoking status and average body mass index (BMI) over the last five years prior to diagnosis, calculated using the Quetelet's index expressed by kg/m^2.

Statistical analyses

Survival time was calculated from date of surgery to the date of death or October 2004. The women, who died of other causes than ovarian cancer, were censored at date of death. Survival differences by previous sterilisation and number of lifetime ovulations were illustrated by Kaplan-Meier curves. We used the Cox proportional hazard model to evaluate the prognostic value of the risk factors. The effect on risk of ovarian cancer death was estimated by hazard ratios (HR) and 95% confidence intervals (95% CI). All analyses were controlled for known prognostic factors according to the literature, including current age (linear), residual disease after primary surgery (no residual disease, debulked but present residual disease, or debulking impossible but biopsies were taken) and type of first-line chemotherapy (platinum-based or no platinum-based), histological type of tumour (serous or other), as well as for smoking status and BMI over the last five years prior to diagnosis, formerly shown to have independent significant impact on prognosis in Stage III ovarian carcinomas [11]. Linearity of the associations with the continuous variables (current age, age at menarche/first childbirth/menopause, years since last childbirth/ sterilisation/hysterectomy, total years of oral contraceptive use and total breastfeeding time, number of ovulation years and BMI) was investigated using a linear spline model. Except for BMI (showing a U-shaped association), no deviations from linearity were seen.

Results

Selected characteristics of the 295 women included in the study are shown in Table 1. Serous adenocarcinomas were the most common histological subtype (n = 225). The majority of women had a non-radical debulking surgery (n = 217), whereas 258 women received platinum-based chemotherapy (Table 1). Overall, 34.9% (n = 103) of the women were overweight five years prior to diagnosis, and 90 women were current smokers.

A total of 21 women had a past history of sterilisation, while 39 women previously had been hysterectomised. Only three women had a past history of both sterilisation and hysterectomy. Fewer women had died of ovarian

Table 1. — *Characteristics and survival time of the 295 women with epithelial ovarian cancer (OC) Stage III included in the study by selected variables.*

Variables	n	% dead of OC	Median survival time in years (95% CI)
Age at diagnosis (years)			
< 50	61	(77.0)	3.8 (2.9-5.0)
50-59	101	(81.2)	2.8 (2.2-3.6)
60-69	77	(81.8)	2.2 (1.7-2.9)
70-79	56	(94.6)	1.2 (1.0-1.9)
Histological type			
Serous adenocarcinomas	225	(82.2)	2.8 (2.3-2.9)
Mucinous adenocarcinomas	15	(93.3)	1.3 (0.9-1.8)
Endometrioid adenocarcinomas	16	(87.5)	2.4 (1.7-4.4)
Clear cell neoplasms	10	(80.0)	2.9 (0.8-4.3)
Papillary adenocarc. NOS	24	(83.3)	1.1 (0.8-2.0)
Undifferentiated carcinomas	5	(80.0)	1.1 (0.6-na.)
Primary surgery radical			
Yes	31	(51.6)	7.2 (4.3-n.a.)
No	217	(84.3)	2.4 (2.1-2.8)
No - only biopsies taken	46	(97.8)	1.3 (0.9-2.2)
Unknown	1	(100.0)	na.
Platinum-based chemotherapy			
Yes	258	(81.0)	2.8 (2.4-3.0)
No	37	(97.3)	0.8 (0.4-1.1)
Body Mass Index (kg/m²)			
< 18.5 (underweight)	12	(83.3)	2.2 (1.2-3.3)
18.5-24.9 (normal-weight)	176	(77.8)	2.8 (2.3-2.9)
≥ 25.0 (overweight)	103	(92.2)	2.1 (1.6-2.7)
Unknown	4	(75.0)	0.7 (0.2-na.)
Smoking status			
Never smoker	126	(81.8)	2.7 (2.3-2.9)
Former smoker	78	(82.1)	2.5 (1.9-3.5)
Current smoker	90	(85.6)	2.0 (1.6-2.5)
Unknown	1	(100.0)	na.
Ever sterilised			
No	274	(84.3)	2.3 (2.0-2.8)
Yes	21	(66.7)	4.3 (2.3-9.1)
Ever hysterectomised			
No	255	(84.3)	2.4 (2.0-2.8)
Yes	39	(74.4)	2.3 (1.9-5.1)
Unknown	1	(100.0)	na.
Age at menarche			
< 13	78	(84.6)	2.3 (1.4-2.9)
13	83	(81.9)	2.5 (1.9-2.9)
14	66	(89.4)	2.3 (1.9-3.1)
> 14	68	(76.5)	2.8 (1.8-4.1)
Age at natural menopause			
< 48 years	35	(91.4)	2.8 (1.2-4.2)
48-49 years	24	(83.3)	2.2 (1.4-4.0)
50-51 years	27	(85.2)	1.1 (0.8-3.0)
≥ 52 years	39	(87.2)	2.7 (2.0-3.1)
Unkwnon	5	(100.0)	1.3 (0.7-4.1)
Artificial causes of menopause	101	(81.1)	2.2 (1.7-2.8)
Premenopausal	64	(76.6)	3.3 (2.5-4.3)
No. of childbirths			
0	47	(80.9)	2.7 (1.7-3.5)
1	55	(83.6)	2.3 (1.7-2.9)
2	123	(82.9)	2.5 (2.2-3.0)
≥ 3	70	(84.3)	2.2 (1.5-3.4)
Ever oral contraception			
No	162	(84.0)	2.1 (1.7-2.5)
Yes	133	(82.0)	2.9 (2.3-3.8)
Ovulation time (years)			
< 30	65	(78.5)	3.4 (2.9-4.4)
30-34	60	(91.7)	1.9 (1.5-2.7)
≥ 35	55	(89.1)	2.4 (1.8-2.8)
Unknown	115	(78.3)	2.2 (1.8-2.8)

NA: not applicable.

cancer if previous pelvic surgery had been performed, though no difference in median survival time was found among hysterectomised and non-hysterectomised women (Table 1). However, women with previous sterilisation were younger at time of ovarian cancer diagnosis (median 54.8 years; 5-95 percentiles: 41.8-72.6 years), while previously hysterectomised women tended to be older (median 63.5 years; 5-95 percentiles: 47.6-77.0 years) than the overall study population (median 59.0 years; 5-95 percentiles: 44.0-76.7 years) (data not shown).

Overall, 231 women were postmenopausal at the time of diagnosis, and in 54% of these an exact menopausal age could be stated, as the time of the menopause was not influenced by e.g. hysterectomy or HRT. Median age at menarche and menopause was respectively 13 years (5-95 percentiles: 11-16 years) and 50 years (5-95 percentiles: 42-56 years) (data not shown). The total number of ovulation years could be estimated in 180 women (61.0%) and the median ovulation time was 32.4 years (5-95 percentiles: 21.6-39.6 years) (data not shown).

According to Kaplan-Meier survival curves, sterilised women seemed to have a better survival (Figure 1a). Similarly, survival tended to be longer with decreasing lifetime number of ovulations, categorized into three groups with cutoff points corresponding to the tertiles (Figure 1b).

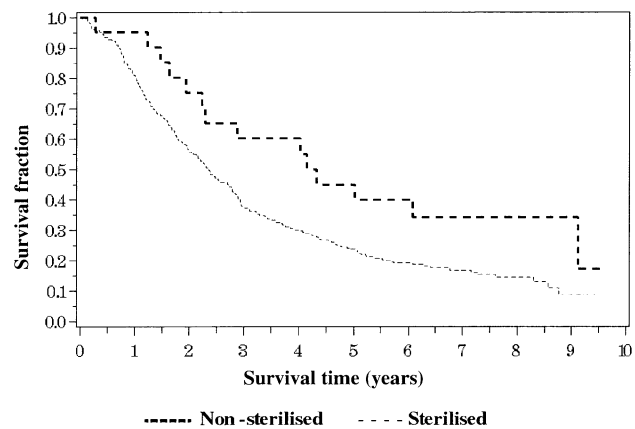

Fig. 1a

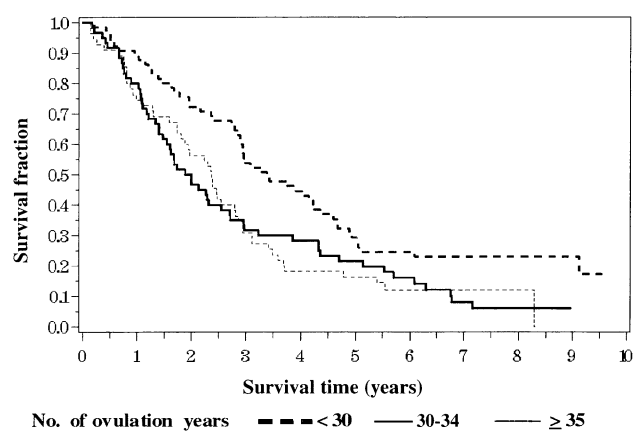

Fig. 1b

Figure 1. — Survival after ovarian cancer by past history of sterilisation (Figure 1a) and by lifetime number of ovulation-years.

Table 2. — *Hazard ratios (HR) and 95% confidence intervals (CI) for ovarian cancer specific death according to previous pelvic surgery and reproductive variables.*

Variables	Adjusted HR (95% CI)[a] n = 294 Stage III	Adjusted HR (95% CI)[b] n = 290 Stage III
Previous pelvic surgery		
Ever sterilised		
No	1.00 (Reference)	1.00 (Reference)
Yes	0.70 (0.41-1.22)	0.62 (0.36-1.08)
Ever hysterectomised		
No	1.00 (Reference)	1.00 (Reference)
Yes	0.66 (0.45-0.98)	0.82 (0.55-1.21)
Reproductive history		
Increasing age at menache		
Continuous per year	0.85 (0.66-1.10)	0.91 (0.84-0.99)
Increasing age at menopause		
Continuous per year	1.02 (0.97-1.07)	1.02 (0.97-1.08)
No. childbirths		
0	0.82 (0.55-1.22)	0.87 (0.59-1.30)
1	1.09 (0.76-1.55)	1.04 (0.73-1.49)
2	1.00 (Reference)	1.00 (Reference)
≥ 3	0.97 (0.69-1.34)	0.87 (0.62-1.22)
Ever oral contraception		
No	1.00 (Reference)	1.00 (Reference)
Yes	0.90 (0.67-1.21)	0.81 (0.60-1.10)
Increasing ovulation time		
Continuous per 10 year	1.47 (1.06-2.05)	1.53 (1.09-2.14)

a) adjusted for current age (linear), residual tissue (no/yes-but debulked/yes-just biopsies taken), histology (serous/other) and platinum-based chemotherapy (yes/no).

b) adjusted for current age (linear), residual tissue (no/yes-but debulked/yes-just biopsies taken), histology (serous/other), platinum-based chemotherapy (yes/no), body mass index (linear spline with a break at 18.5 kg/m^2) and smoking status (current/former/never)

Cox regression models were adjusted for the potentially confounding factors including age, stage, radicality of primary surgery, treatment with platinum-based chemotherapy, histology, BMI over the last five years prior to diagnosis and smoking status at diagnosis. The hazard ratios of ovarian cancer specific death related to past history of sterilisation, hysterectomy and reproductive factors are shown in Table 2. Histological grade and sub-stage (IIIa, b, c) had no prognostic impact on ovarian cancer survival, and adjustment for grade and sub-stage did not affect the estimates for past history of pelvic surgery and reproductive variables (data not shown). On a subgroup of cases (~50%), we also had information about performance status at start of chemotherapy. However, adjustment for this covariate did not change the estimates of previous pelvic surgery and the reproductive variables (data not shown).

Past history of sterilisation and of hysterectomy seemed to decrease the risk of ovarian cancer death (HR = 0.62; 95% CI: 0.36-1.08 and HR = 0.82; 95% CI: 0.55-1.21 when adjustment included BMI and smoking status), although none of these associations reached statistical significance. Risk of ovarian cancer death decreased 4% per year since sterilisation (HR = 0.96 per year; 95% CI: 0.90-1.01, p = 0.11) (data not shown), while increasing time since hysterectomy seemed to slightly increase risk of ovarian cancer death (HR = 1.02; 95% CI: 0.98-1.06, p = 0.35).

Increasing age at menarche was associated with a decreased risk of ovarian cancer death (HR = 0.91 per year; 95% CI: 0.84-0.99), while increasing age at menopause tended to slightly increase the risk. Parity had no impact on ovarian cancer specific survival (Table 2); neither did number of pregnancies or abortions, age at first childbirth, time since last childbirth or the total time of breastfeeding periods (data not shown).

Use of oral contraceptives seemed to be associated with decreased risk of ovarian cancer specific death (HR = 0.81; 95% CI: 0.60-1.10), though the cumulative time of oral contraceptive use had no significant impact on ovarian cancer survival (data not shown).

Among women where the total number of ovulation years could be estimated (n = 180), an association between increasing number of ovulation years and risk of ovarian cancer death was found (HR = 1.53 per 10 years; 95% CI: 1.09-2.14). Even though the test for linearity allowed analyses of the number of ovulation years as a linear variable, the effect tended to level off at high number of ovulation years (data not shown). The association between lifetime number of ovulation years and risk of ovarian cancer specific death remained significant when adjustment also included ever sterilisation, parity and ever oral contraceptive use (HR = 1.49 per 10 years; 95% CI: 1.03-2.16, data not shown).

Discussion

Several tumour and treatment related prognostic variables for ovarian cancer survival have been identified (e.g., stage, residual disease, histological grade and chemotherapy), but only few patient-related prognostic factors are known (e.g., age and performance status) [12]. The purpose of our study was to investigate the prognostic impact of epidemiological risk factors for survival following ovarian cancer.

Our results, based on 295 women with Stage III epithelial ovarian cancer, show that epidemiological determinants for development of ovarian cancer only have minor prognostic impact on survival following ovarian cancer. However, the prognostic impact of the examined variables followed the same pattern as the impact of the variables on ovarian cancer development. Factors associated with decreased risk of ovarian cancer development also seemed to be associated with decreased risk of ovarian specific death (e.g. sterilisation, hysterectomy, oral contraception use, and increasing menarche age), and risk factors for development of ovarian cancer also seemed to be associated with increased risk of ovarian cancer specific death (e.g., increasing age at menopause and total time of ovulation). However, parity had no prognostic impact.

Our results on the prognostic impact of past history of sterilisation are in contrast to the results of Naik [5], who found that sterilised women with Stage III epithelial ovarian cancer had decreased survival. However, these results were based on only eight sterilisations among 140 women. In our larger study population, survival seemed to be improved among women with a past history of ster-

ilisation and the same pattern was found for hysterectomy. As we only adjusted for residual disease after the primary surgery in an overall way, not distinguishing between size and number of residual lesions after the debulking surgery, it is possible that previously hysterectomised women had less tumour burden at the time of ovarian cancer diagnosis and after surgery as well, as no potentially non-removable tumour-infiltrated uterus was present. However, this can not explain the protective effect of previous sterilisation observed in our study. It has been suggested that tubal ligation results in changes in ovarian blood flow [13] and suppression of ovarian hormone production followed by increased number of anovulatory cycles. This may explain the decreased risk of ovarian cancer development following tubal ligation and may also result in development of ovarian cancer types with a better prognosis. However, the literature on the effect of tubal ligation is very inconsistent [14-16].

Few studies have examined the association between reproductive risk factors and survival following ovarian cancer, resulting in either weak or random associations, or more often no associations. We found that higher age at menarche was associated with improved survival. This was, however, not found by others [6, 8]. Schneider *et al.* [6] found that multi-gravidity was associated with improved survival; we and others did not find such an association [7, 8]. Jacobsen *et al.* [7] found that the number of abortions had a prognostic impact; we could not confirm such an association. Neither we, nor Zhang *et al.* [9] found that use of oral contraceptives had significant impact on survival following ovarian cancer. It therefore seems as though the prognostic impact of the individual reproductive variables is negligible; if existing at all. Similarly, no association between survival following breast cancer and factors affecting the risk of developing breast cancer has been found [17].

By calculating the total lifetime number of ovulations, we accumulated the possible minor effects of the reproductive variables and found that survival decreased significantly with increasing number of ovulations. It has been suggested that repetitive ovulations may induce mutations resulting in more aggressive tumours [18]. This is in agreement with the 'incessant ovulation' theory of Fathalla [19], where an increasing number of lifetime ovulations is a causal factor in ovarian cancer. We can, however, not exclude that bias were introduced by restricting this analysis to a selected subgroup of women in whom estimation of the total number of ovulations was possible. We found, however, the same prognostic impact pattern of the variables analysed in the subgroup compared to the complete study group.

Some strengths and limitations of the study should be considered: We followed prospectively a well-characterized ovarian cancer study population, resulting in a long-term follow-up of five to nine years with no patients lost to follow-up. Information on the epidemiological variables was specifically asked for at a personal interview, and not obtained from retrospective reviews of patient files. However, recall bias can not be excluded. The study population was homogenous with regard to stage, as we focused on Stage III patients only. We actually also tested the prognostic effect of the variables among women with Stage I disease (n = 157), finding that only age and substage (IA vs IC) had a prognostic impact (data not shown). The number of patients with Stage II and IV disease was too few to perform a reliable survival analysis.

In conclusion, our study covering five to nine years follow-up on 295 Stage III ovarian carcinoma patients showed that increasing lifetime number of ovulations had a negative impact on survival following ovarian cancer. In addition, past history of sterilisation seemed to be associated with an improved prognosis following ovarian cancer, whereas the individual reproductive risk factors had no independent impact on prognosis.

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